

CHAPTER 3

Amenorrhea

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Patients with amenorrhea can be classified as “primary” (absence of menses in a 14-year-old who has failed to develop any secondary sexual characteristics, or in a 16-year-old who has had otherwise normal development) or “secondary” (lack of menses in a woman who previously menstruated and has missed either three normal cycles or has had 6 months of amenorrhea).

After evaluation for pregnancy it is helpful to categorize patients with primary or secondary amenorrhea based on sex hormone production, which may be normal, increased, or decreased. For instance, a primary amenorrhea patient with müllerian dysgenesis would have normal sex hormone levels, whereas a Turner syndrome patient would have low estrogen and progesterone with correspondingly high gonadotropins. Sex steroid levels (17-hydroxyprogesterone) are high in patients with congenital adrenal hyperplasia.

Any diagnosis that can present as secondary amenorrhea can also present as primary amenorrhea. The first step is a physical examination focused on signs of malnutrition, abnormal growth and development, an anatomically intact reproductive tract, central nervous system (CNS) disease, and galactorrhea.

PRIMARY—GENETICS/ENDOCRINE

Symptoms

- Failure of onset of menses (by age 14 in patients without development of secondary sexual characteristics; age 16 with normal development)
- Monthly abdominal pain without menstruation (suggests an imperforate hymen or transverse vaginal septum)
- Abnormal body hair distribution (virilizing)

Signs

- Galactorrhea
- Hirsutism

Workup

- Physical examination for developmental anomalies. The examiner should particularly be alert to findings consistent with an imperforate hymen, vaginal aplasia, or Turner syndrome (short

stature, webbed neck and a “shield” chest deformity [all +++++]). Assignment of a Tanner stage should be documented.

- Pregnancy testing
- TSH and prolactin level
- Pelvic ultrasound if necessary to document presence of the uterus
- Imaging of the sella turcica if galactorrhea present by history or exam



ANOVULATION: SEE SECONDARY AMENORRHEA



CONGENITAL ADRENAL HYPERPLASIA

Signs

- Most cases are detected before puberty and are partial 21-hydroxylase deficiency. +++++
- Mild forms present as a short-statured individual. +
- Early epiphyseal closure demonstrated on x-rays for bone age +++++



POLYCYSTIC OVARY SYNDROME (PCOS) AND ANDROGEN-SECRETING TUMORS: SEE SECONDARY AMENORRHEA



PSEUDOHERMAPHRODITISM

Signs

- These individuals have 46, XY genetics but are phenotypically female due to deficient androgen production or androgen resistance at the tissue level.



TURNER SYNDROME

Signs

- 45, XO genetics
- Patients appear to have Turner syndrome but have pure X,O genetics, while others are mosaics or have structural abnormalities of either an X or Y chromosome. +++
- Gonadal dysgenesis +++++

Symptoms

- Low neck hairline +++++
- Webbed neck +++++
- A high-arched palate +++++
- Aortic coarctation +++
- Hearing loss ++

SECONDARY AMENORRHEA

The traditional approach has been to localize the organ system responsible for the amenorrhea (hypothalamus, pituitary, ovary, or uterus), then zero in on the specific problem. The majority of cases have a simple solution, with only the occasional referral necessary for diagnosis or treatment.



HYPOTHALAMIC-PITUITARY-OVARIAN AXIS

The hypothalamic-pituitary-ovarian axis is a way of referring to the combined effects of the hypothalamus, pituitary gland, and ovaries. The hypothalamic-pituitary-ovarian axis is a critical part in the development and regulation of the reproductive system.

The pathway begins with gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus. GnRH acts on the anterior pituitary, causing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the bloodstream. LH and FSH both act on the ovaries causing secretion of estrogen and progesterone. Estrogen and progesterone then act on the uterus, regulating the growth and sloughing of the endometrial lining in a cyclical fashion.

Hormone release in the hypothalamic-pituitary-ovarian axis is regulated by a negative feedback mechanism. Estrogen and progesterone can provide negative feedback to the anterior pituitary and hypothalamus. Stimulation and regulation complete the pathway among hypothalamus, pituitary, and ovaries.

Symptoms

- Amenorrhea (in the absence of pregnancy)
- Galactorrhea (secretion of milky fluid from one or both breasts in a nulliparous woman or one whose last pregnancy or weaning is more than 12 months prior) +
- Hair growth in a virilizing pattern +

Signs

- Loss of menstrual function for at least 3 months (the sine qua non for diagnosis)
- Galactorrhea +
- Hirsutism +

Workup

- On physical examination, normal vaginal mucosal appearance and presence of thin, mucoid secretions is indicative of the presence of adequate estrogen.
- Pregnancy testing
- TSH
- Serum prolactin level—Hyperprolactinemia is present in the majority of patients presenting with amenorrhea and galactorrhea. ++++ Prolactin levels greater than 300 ng/mL virtually always denote a prolactinoma.
- Imaging of sella turcica, if galactorrhea present or prolactin level elevated
- If the examination, pregnancy test, TSH, prolactin and imaging of the sella turcica are normal, administer 10 mg oral medroxyprogesterone acetate (Provera, others) for 5 days. Onset of menses within a week after treatment confirms an intact genital tract and the presence of endogenous estrogen. At this point, the management of the patient centers around whether conception is desired. If not, a monthly 5-day course of progestin will suffice to eliminate the increased risk of endometrial cancer.
- The absence of withdrawal bleeding following progestin necessitates administration of estrogen for 21 days, concurrent with progestin for the final 5 days. Ensuing menstruation confirms an intact reproductive tract and an absence of endogenous estrogen. Gonadotropin levels (FSH, LH) are then indicated.

Comments and Treatment Considerations

Amenorrhea traumatica: Often referred to as Asherman syndrome, which constitutes endometrial scarring and synechiae from prior instrumentation. Scarring may also be present from prior infectious processes. These patients have normal sex hormone levels.

Anovulation: Other than pregnancy, the most common cause of secondary amenorrhea. This diagnosis has been established when a patient with normal TSH and prolactin levels has a withdrawal bleed after supplemental progesterone challenge. Women who do not currently desire conception can be treated with conventional oral contraceptive pills (OCPs) or with monthly progesterone (10 mg daily for 10 days), and should be instructed to present for reevaluation if they have return of amenorrhea. If conception is desired, evaluation for polycystic ovary syndrome (PCOS) should be considered prior to any attempt at induction of ovulation.

Emotional stress/illness: Low gonadotropins result from dysfunction of the hypothalamic/pituitary axis in patients with anorexia nervosa or excessive exercise +++++ in women at or less than 22% body fat, in addition to many endocrine diseases such as thyroid dysfunction and adrenal insufficiency.

Hyperprolactinemia: A pituitary tumor secreting prolactin will, in virtually every case, be accompanied by low gonadotropin levels. A “coned-down” view of the sella turcica is an excellent,

quick, and inexpensive screening tool, whereas CT or MRI can give more definitive information. Many accept that patients with small prolactin-secreting tumors with serum prolactin levels less than 100 ng/mL may be managed conservatively with bromocriptine. Large tumors with prolactin levels greater than 300 ng/mL are unlikely to respond; with levels less than 100 ng/mL, a large tumor is probably not a prolactin-secreting mass and neurosurgical referral is indicated.

Ovarian failure: A woman who fails to have a withdrawal bleed after progesterone administration either does not have endogenous estrogen (necessary to create proliferative endometrial changes) or has a uterine defect. Simple evaluation for this scenario is described above ("workup").

Autoimmune ovarian failure is not uncommon. Initial workup (after demonstrating elevated gonadotropins) should include CBC, metabolic panel including calcium and phosphorus, thyroid studies, serum proteins, antinuclear antibody (ANA), and rheumatoid factor.

Other possible etiologies for early ovarian failure include radiation changes, chemotherapeutic agents, surgery, malignancy, infection and interruptions in vascular supply to the ovaries. Ovarian tumors producing androgens will *suppress* FSH and LH levels, resulting in amenorrhea.

A young woman diagnosed with ovarian failure (secondary amenorrhea with elevated gonadotropins) should be referred for consideration of gamete intrafallopian transfer (GIFT) or other fertility measures if desired.

The unusual scenario of low gonadotropins in the setting of secondary amenorrhea should prompt further evaluation for hypothalamic and/or pituitary failure, including CNS imaging even in the absence of an elevated prolactin level.

PCOS: Sometimes referred to as Stein-Leventhal syndrome, these patients are anovulatory +++++ and have hirsutism +++ and obesity +++. Ultrasound demonstrates enlarged, cystic ovaries. ++++ An elevated LH/FSH ratio is commonly seen. +++++. Test these patients for glucose intolerance (SORT "C").

PREGNANCY

Pregnancy and age-appropriate ovarian failure are the only normal physiologic causes of amenorrhea. Because pregnancy is the most common cause of amenorrhea and the easiest to diagnose, testing for pregnancy should be carried out as the initial evaluation in all cases of amenorrhea.

Symptoms

- Breast tenderness ++
- Nausea ++
- Sensation of fetal movement (+++ beyond 18 weeks' gestation)

Signs

- Enlargement of the abdomen (beyond first trimester)
- Cervical softening
- Bluish discoloration of vaginal mucosa (Chadwick's sign) ++++
- β -hCG detection in plasma or urine +++++
- Detection of fetal heartbeat by Doppler or ultrasound (+++++ beyond 12 weeks)
- Perception of fetal movement by examiner

Workup

- Pregnancy testing: Plasma and urinary levels are detectable prior to a missed menses, as early as 7 to 10 days after conception. Urine tests commonly available have a threshold for detecting hCG of 20 mIU/mL (plasma tests are 10 mIU/mL); by day 7 to 10 postconception, typical urine levels are 25 mIU/mL. A first-morning urine has the greatest concentrations of hCG.
- Ultrasound: In normal pregnancy a gestational sac should be visible with vaginal scanning when the hCG level is 1800 or greater (exact number varies between institutions). Ectopic pregnancy can occur at any level of β -hCG. Absence of definitive signs of pregnancy at β -hCG levels above the institutional threshold are very concerning for the possibility of ectopic pregnancy.

Comments and Treatment Considerations

Note: Any patient with a positive β -hCG who is hemodynamically unstable should have immediate surgical evaluation for ectopic pregnancy!

In addition to ectopic pregnancy, many pregnancy-related conditions may present with vaginal bleeding. The absence of amenorrhea therefore does not necessarily rule out pregnancy. A recent menstrual history, in addition to pregnancy testing, is essential to the evaluation of all patients with abnormal vaginal bleeding.

Elevated hCG levels may also be present in trophoblastic and non-trophoblastic disease; the possibility of these conditions should be considered before a diagnosis of pregnancy is given.

Establishment of a diagnosis of intrauterine pregnancy terminates the workup for amenorrhea. The hormonal manipulation described previously in the evaluation of a preexisting secondary amenorrhea is not possible (nor advised!) during pregnancy. Important areas for discussion between practitioner and patient in the setting of pregnancy include:

- Clear evidence supporting the cessation of smoking and alcohol use, and the expert consensus on cessation of recreational drug use
- Medications to avoid or discontinue during pregnancy
- Identification of providers for prenatal care and delivery, as well as for any preexisting medical conditions that complicate pregnancy (e.g., hypertension, diabetes, thyroid disease)
- Nutrition during pregnancy, including periconception folate supplementation to prevent neural tube defects

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